Vandetanib Plus Chemotherapy for Induction Followed by Vandetanib or Placebo As Maintenance for Patients with Advanced Non–Small-Cell Lung Cancer

A Randomized Phase 2 PrECOG Study (PrE0501)

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Introduction: After early reports of vandetanib's efficacy in the induction setting, we evaluated the effect of combination docetaxel, carboplatin, and vandetanib, followed by maintenance therapy with either vandetanib, or placebo on progression-free survival (PFS) in patients with advanced non–small-cell lung cancer.

Methods: Patients with advanced non–small-cell lung cancer were randomized to induction docetaxel (75 mg/m^2) + carboplatin (area under the curve of 6) on day 1 of a 21-day cycle, and daily vandetanib (100 mg/day orally) for four cycles, followed by daily vandetanib (300 mg/day orally) or placebo until progression. Eligible patients had measurable disease, Eastern Cooperative Oncology Group performance status 0 of 1, and no prior cytotoxic or targeted agents for advanced disease.

Results: One hundred sixty-two patients were randomized; 158 began induction treatment. Fifty-eight patients began maintenance vandetanib or placebo (median, 3.5 cycles). Median PFS for patients randomized to maintenance vandetanib was 4.5 months (95% confidence interval, 3.3–5.8 months), and for patients randomized to maintenance placebo was 4.2 months (95% confidence interval, 2.8–4.9 months). An exploratory analysis showed prolonged PFS for patients randomized to vandetanib maintenance (stratified log-rank p= 0.07) as also in a multivariate model adjusting for sex and stage (p = 0.02). Differences in PFS were not observed among patients who began maintenance therapy. Toxicities were similar to other studies of these agents.

Conclusion: Neither arm showed improvement over historical median PFS of 4.6 months, although patients who began maintenance and were randomized to vandetanib had somewhat better outcomes than those randomized to placebo. Given its acceptable toxicity profile, there may be a role for vandetanib in maintenance.

Key Words: Vandetanib, Non–small-cell lung cancer, Maintenance therapy.

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Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 159,480 deaths predicted for 2013.[1] Over 80% of these patients have non–small-cell lung cancer (NSCLC); most have advanced disease at diagnosis. Patients with advanced disease and good performance status (PS) clearly benefit from chemotherapy. Many clinical trials testing for the most effective regimen demonstrated that all platinum-based doublets produce similar results. Trials with additional agents have been disappointing; the majority of these studies demonstrated increased toxicity without additional benefit in survival.[2–5] The poor outcomes associated with advanced NSCLC demonstrate the need for continued improvements in treatment.

In recent years, strategies tested targeting the vascular endothelial growth factor (VEGF) pathway, and in a phase III Eastern Cooperative Oncology Group (ECOG) trial (E4599), patients with advanced NSCLC who received carboplatin + paclitaxel with bevacizumab[6] demonstrated improved median overall survival (OS) (p = 0.003) compared with patients who received chemotherapy alone.

The epidermal growth factor receptor (EGFR) pathway has been yet another therapy target. Studies have shown shortened OS in NSCLC patients whose tumor overexpresses EGFR.[7–9] EGFR inhibitors have

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demonstrated utility as salvage therapy,[10] and more recently, as maintenance agents.[11] The association between *EGFR* mutations and clinical benefit was also emerging at the time the study was designed, although mutation status was not being used to select patients for treatment at that time.[12,13]

Given evidence of activity in targeting the VEGF and EGFR pathways, investigators tested the simultaneous targeting of both pathways in the previously treated, recurrent NSCLC setting[14] in a phase I/II trial using bevacizumab plus erlotinib. This combination was well tolerated and encouraging levels of activity were observed. On the basis of these findings, randomized phase III studies had been launched and were nearing completion of accrual at the time this study was designed.[15,16]

Vandetanib is a novel oral tyrosine kinase inhibitor with dual activity against both the VEGFR and EGFR pathways. Preliminary studies of vandetanib in NSCLC demonstrated sufficient activity to warrant further clinical investigations. The combination of docetaxel and vandetanib had been studied in a randomized phase II trial of 127 patients with NSCLC who were previously treated and failed first-line therapy for metastatic or advanced disease.[17] Patients were treated with docetaxel alone versus two dosages (300 mg or 100 mg daily orally [PO]) of vandetanib. Patients who received docetaxel plus vandetanib at 100 mg PO daily had fewer toxicities and equal efficacy compared with patients on higher dosage of vandetanib, and when compared with docetaxel alone, experienced prolonged progression-free survival (PFS). We undertook this study to evaluate the combination of docetaxel + carboplatin and vandetanib, followed by maintenance of vandetanib or placebo given until disease progression. Given the demonstrated value of EGFR-directed chemotherapy for maintenance, and the proven value of targeting VEGF, we posed the question for the role of this dual inhibitor during maintenance.

PATIENTS AND METHODS

Patients and Eligibility Criteria

Eligible patients had primary or recurrent, advanced (stage IIIB or IV) NSCLC measurable by Response Evaluation Criteria in Solid Tumors criteria (version 1.0).[18] Patients with any histologic subtype were eligible, including squamous cell carcinoma. Previous cytotoxic chemotherapy or targeted therapy for advanced or metastatic disease was not allowed; however, postoperative adjuvant therapy for NSCLC was allowed, provided the last dosage was administered at least a year before randomization, with current evidence of disease progression. Other inclusion criteria included ECOG PS of 0 or 1, age 18 years or more, and adequate organ function, including normal calcium and magnesium. Ineligibility criteria included cardiac dysfunction, greater than grade 1 neuropathy or known sensitivity to carboplatin.

The trial was approved by site institutional review boards and was registered in clinicaltrials.gov (NCT 00687297).

Treatment

Patients were randomized before induction. For patients randomized to either arm, the 21-day cycles 1 through 4 (induction) consisted of pretreatment with dexamethasone, then docetaxel, administered intravenously over 1 hour at a dosage of 75 mg/m^2 on day 1, and carboplatin administered over 15 to 30 minutes at an area under the curve (AUC) of 6 immediately following docetaxel on day 1, and 100 mg PO of vandetanib daily. Commercially available docetaxel and carboplatin were used.

Patients discontinued treatment for evidence of disease progression or unacceptable toxicity. Patients with improved or stable disease after four cycles could continue to the maintenance phase. During maintenance, patients received blinded study drug, either 300 mg/day of vandetanib or placebo PO. Maintenance therapy was administered until progression.

Safety was evaluated using National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3. Before each cycle, laboratory levels were checked, and a physical examination, including recording blood pressure, was conducted. An electrocardiograph was done at baseline, at 3-month intervals, and at the end of treatment. Dosage modifications for neutropenia, thrombocytopenia, hypertension, QTc prolongation, hepatic toxicity, edema, and skin toxicities were specified in the protocol.

Study Efficacy Endpoints and Assessment of Response

The goal of the trial was to study the combination of docetaxel + carboplatin and vandetanib, followed by maintenance of vandetanib or placebo until disease progression, to determine whether active maintenance therapy could prolong PFS. PFS was defined as time from randomization to disease progression or death from any cause. Patients alive and disease free at the time of analysis were censored at the date of last disease evaluation. A secondary endpoint was overall response, measured using Response Evaluation Criteria in Solid Tumors[19] Version1.0. OS was defined as time from randomization to death. Patients alive at the time of this report were censored at the date of last contact.

Randomization and Masking

Randomization used permuted blocks within strata, where strata were combinations of sex (male versus female) and stage (IIIB versus IV/recurrent). Randomization code lists were prepared by the study statistician. Open-label vandetanib and blinded study drug were shipped to each site for induction and maintenance, respectively. Bottle numbers for blinded study drug were allocated to vandetanib and placebo by the study statistician.

Statistical Methods

Standard therapy (docetaxel/carboplatin) was expected to confer median PFS of 4.6 months. The addition of vandetanib, with chemotherapy, and in addition, as maintenance therapy, would be considered worthy of further study if median PFS was 6.2 months or more. Assuming accrual of 7.25 eligible

patients per month for 21 months (152 total eligible patients), and 8 months of additional follow-up, the study would have 90% power, using an exponential test with one-sided type I error of 10%. To allow for 5% ineligibility, a total accrual of 160 patients was planned. Full information would exist when 64 of 76 patients on either arm either progressed, or died. In case of improvement demonstrated over historical control for both arms, the added benefit conferred by maintenance vandetanib was to be evaluated using a stratified log-rank test among patients who received four cycles of induction. Full information required 73 progression events among an assumed 93 qualifying patients; there was 80% power to detect 50% improvement.

An interim safety analysis was planned after 15 patients completed induction. The design called for suspension if any of the following were observed: any grade 5 events, five or more unexpected events, or five or more treatment-related occurrences of grade 3 or higher of rash, diarrhea, hypertension, dehydration, or QTc prolongation.

Descriptive statistics were used to characterize patients at baseline. In addition to the analyses described above, there were protocol-specified analyses of outcomes by sex and age. We also constructed multivariate Cox proportional hazards models of PFS adjusting for significant prognostic factors. Mehta's exact test for ordered categorical data (2-sided) was used to test for differences in toxicity profiles by arm. Stratified log-rank tests used actual assigned strata, even though there were some misstratified patients. Multivariable models used actual patient characteristics rather than stratification factors.

RESULTS

Between May 30, 2008 and November 30, 2009, 162 patients were enrolled by 26 institutions and randomized to induction followed by maintenance with either vandetanib, or placebo. Figure 1 shows disposition of cases (Consolidated Standards of Reporting Trials [CONSORT] diagram). Four patients withdrew before induction because of ineligibility (n = 2) or withdrawal of consent (n = 2). One hundred patients stopped treatment before maintenance; the remaining 58 received maintenance vandetanib or placebo. Patients without progression were followed through 1 year of maintenance. This report reflects the status of the database as of January 28, 2011, when the database was locked and treatment of four remaining patients being treated was unblinded. One was receiving placebo and treatment was stopped. The remaining three patients remained on vandetanib maintenance. Median follow-up among patients still alive is 13.5 months.

Thirty patients did not meet eligibility criteria. The most common reason for ineligibility was missing or out-of-range laboratory values (magnesium, potassium or calcium; n = 24). Other reasons included hypertension (n = 3), incorrect histology (n = 2), and superior vena cava syndrome (n = 1). Ineligible patients were included in all analyses.

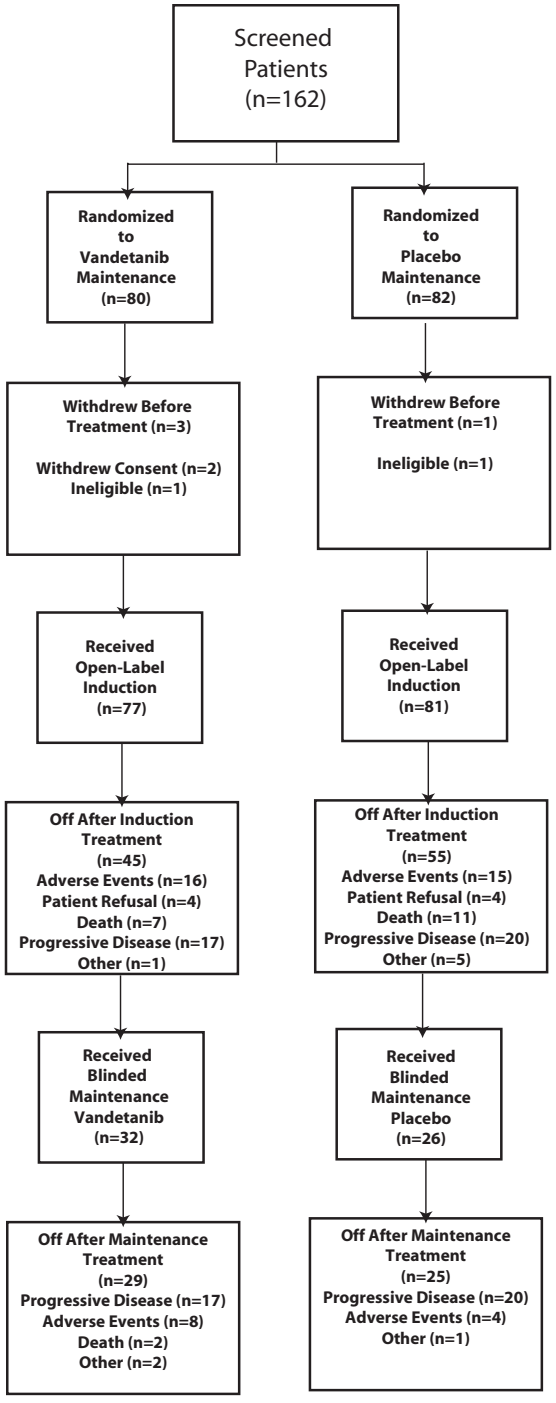

FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

Patient Characteristics

Baseline patient and disease characteristics are shown in Table 1. Median age was 63 years. The most common histology was adenocarcinoma. The proportion of patients with stage IV or recurrent disease was slightly higher than anticipated (91%). Seven patients with stage IV or recurrent disease (5 on vandetanib maintenance, 2 on placebo maintenance) were incorrectly stratified as having stage IIIB disease. Both arms were well balanced with respect to this and other potentially prognostic factors.

TABLE 1. Baseline Patient and Disease Characteristics

	Vandetanib Maintenance	Placebo Maintenance	Total
Total patients	80	82	162
Age, median (range)	63.5 (38–84)	63 (36–82)	63 (36–84)
Age, yr	*n* (%)	*n* (%)	*n* (%)
<50	10 (12.5)	6 (7.3)	16 (9.8)
50–59	16 (20.0)	26 (31.7)	42 (25.9)
60–69	34 (42.5)	23 (28.1)	57 (35.2)
≥70	20 (25.0)	27 (32.9)	47 (29.0)
Sex			
Male	42 (52.5)	42 (51.2)	84 (51.9)
Female	38 (47.5)	40 (48.8)	78 (48.2)
Race/ethnicity			
White, non-Hispanic	66 (82.5)	72 (87.8)	138 (85.2)
White, Hispanic	0	2 (2.4)	2 (1.1)
Black, non-Hispanic	9 (11.3)	8 (9.8)	17 (9.3)
Black, Hispanic	1 (1.3)	0	1 (0.5)
Asian	1 (1.3)	0	1 (0.5)
Native Hawaiian/Pacific Islander	1 (1.3)	0	1 (0.5)
Other	2 (2.5)	0	2 (1.1)
Stage			
IIIB with malignant effusion	5 (6.3)	9 (11.0)	14 (8.6)
IV	68 (85.0)	66 (80.5)	134 (82.7)
Recurrent	7 (8.8)	7 (8.5)	14 (8.6)
ECOG PS			
0	27 (33.8)	34 (41.5)	61 (37.7)
1	53 (66.3)	48 (58.5)	101 (62.4)
Histology			
Adenocarcinoma	46 (57.5)	48 (58.5)	94 (58.0)
Squamous cell carcinoma	19 (23.8)	16 (19.5)	35 (21.6)
Large cell carcinoma	4 (5.0)	0	4 (2.5)
Bronchioalveolar	0	3 (3.7)	3 (1.9)
Adenosquamous	2 (2.5)	2 (2.4)	4 (2.5)
NSCLC, NOS	9 (11.3)	12 (14.6)	21 (13.0)
Other	0	1 (1.2)	1 (0.5)
Smoking history			
Ever smoker (*n* = 161)	74 (92.5)	76 (93.8)	150 (93.2)
Current smoker (*n* = 150)	15 (20.3)	32 (27.6)	36 (24.0)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified.

Treatment Administration

A median of three induction cycles was administered. The most common reasons for discontinuation during induction were disease progression (36%), adverse events (30%), and death during study (17%). Fifty-eight patients completed all four cycles of induction and began maintenance. Cumulatively, patients received 462 cycles of induction chemotherapy. Of these, 346 were planned for delivery of carboplatin at AUC 6, 115 at AUC 5, and 1 at AUC 4, and 99% of cycles were delivered at the planned full dosage. Among 462 cycles of docetaxel given, 340 were planned for 75 mg/m^2, 115 were planned for 60 mg/m^2, two were planned for 45 mg/m^2, and two were held. Almost all cycles (98.7%) were administered at the planned full dosage. The most common reason for dosage adjustment was toxicity. Median dosage of vandetanib administered during induction was 100 mg/day, the target dosage.

Among 32 patients randomized to vandetanib maintenance and treated in the maintenance phase, a median of four cycles of maintenance was administered. The most common reasons for treatment discontinuation in this group were disease progression (59%) and adverse events (28%). Three patients were still receiving treatment at the time of database lock. Median dosage of vandetanib administered during maintenance to patients on this arm was 300 mg/day, the target dosage.

Among 26 patients randomized to placebo maintenance who began maintenance, a median of 2.5 cycles was delivered. Treatment was discontinued most commonly because of

disease progression (80%), although four patients (16%) discontinued placebo maintenance because of adverse events. One patient was still receiving placebo at the time of database lock. The difference in duration of maintenance treatment between arms was not statistically significant (2-sided Wilcoxon rank sum $p = 0.62$).

Adverse Events

All treated patients were assessed for adverse events every 21 days during induction, and every 28 days during maintenance. The protocol-specified interim safety analysis was conducted after the first 15 patients were followed long enough to complete induction (4 cycles). We found neither excess serious, unexpected adverse events, nor any higher-than-expected incidence or severity of previously reported events, so the study continued. A second safety analysis was conducted at the request of the Data Safety Monitoring Board, after half the patients were enrolled long enough to complete four cycles of induction. After reviewing those data, the Data Safety Monitoring Board recommended continuation of the study.

Table 2 shows adverse events across all treatment phases, regardless of attribution, by grade and system organ class. Supplementary Tables 1 and 2 (Supplementary Digital Content, http://links.lww.com/JTO/A431) show adverse events of grade 3 and higher in more detail, for induction (treatment-related) and maintenance by arm. The distribution of worst-degree toxicities did not differ by arm ($p = 0.93$). Supplementary Table 3 (Supplemental Digital Content, http://links.lww.com/JTO/A431) shows adverse events reported posttreatment.

There were seven grade 5 treatment-related events during induction, including two infections, two hemorrhages, central nervous system cerebrovascular ischemia, cardiac arrest, and a death described as acute cardiopulmonary arrest, likely secondary to progression of lung cancer and possible aspiration. Four other patients died during induction of adverse events that were not considered treatment related: three from metabolic acidosis and one from dyspnea. Nine patients died of progressive disease during induction and two during maintenance therapy. In addition, one patient died of progressive disease within 30 days of the end of treatment.

We noted several patients for whom diverticulitis was reported. Because diverticulitis is not a recognized term in Common Toxicity Criteria for Adverse Events Version 3, we explored events in the gastrointestinal system in more detail.

TABLE 2. All Adverse Events Regardless of Attribution, by System, Organ, and Class

	Randomized to Vandetanib Maintenance ($n = 77$)					Randomized to Placebo Maintenance ($n = 81$)				
	1	2	3	4	5	1	2	3	4	5
Allergy/immunology	4	5	1	2	—	3	3	2	—	—
Auditory/ear	2	1	—	—	—	1	1	—	—	—
Blood/bone marrow	4	4	9	31	—	1	3	16	28	1
Cardiac arrhythmia	4	3	5	1	—	3	6	7	—	—
Cardiac general	3	3	4	1	2	7	8	3	1	—
Constitutional symptoms	9	27	8	1	—	18	17	14	1	—
Coagulation	—	—	—	—	—	—	—	2	—	—
Dermatology/skin	12	23	13	1	—	11	28	5	2	—
Death	—	—	—	—	5	—	—	—	—	6
Endocrine	2	—	1	—	—	3	1	—	—	—
Gastrointestinal	17	29	15	2	—	17	20	25	1	—
Bleeding/bleeding	15	4	1	—	—	7	3	1	—	2
Hepatobiliary/pancreas	—	—	1	—	—	—	—	1	—	—
Infection	—	10	14	4	—	2	16	10	4	3
Lymphatics	5	6	—	—	—	9	4	1	—	—
Metabolic/laboratory	18	5	12	—	1	9	7	15	3	1
Musculoskeletal/soft tissue	1	3	3	1	—	4	7	4	—	—
Neurology	14	11	9	—	1	13	6	10	—	—
Ocular/visual	3	1	—	—	—	7	3	—	—	—
Pain	15	16	10	2	-	10	19	15	—	—
Pulmonary/upper respiratory	19	6	8	—	1	12	8	12	1	—
Renal/genitourinary	4	—	1	—	1	2	2	3	—	—
Secondary malignancy	—	—	1	—	—	—	—	—	—	—
Sexual/reproductive function	—	1	—	—	—	1	—	—	—	—
Syndromes	1	—	1	—	—	—	2	—	—	—
Vascular	1	2	5	3	—	4	7	3	5	—
Worst degree	1	8	23	34	10	2	8	25	35	11

TABLE 3. Adverse Events Potentially Associated with Diverticulitis

	Randomized to Vandetanib Maintenance		Randomized to Placebo Maintenance	
	Grade 3	Grade 4	Grade 3	Grade 4
Abdomen, pain	1	—	2	—
Colitis	1	—	—	—
Colitis, infectious (e.g., *C.diff*)	1	–	1	–
Diarrhea without previous colostomy	9	–	10	–
Enteritis	1	—	—	—
Fistula, colon/cecum/appendix	—	—	1	—
Gastrointestinal, other	—	1	1	—
Illeus	—	—	1	—
Muco/stomatitis by exam, oral cavity	3	—	—	—
Obstruction, ileum	—	—	1	—
Perforation, colon	1	—	—	—
Upper gastrointestinal, hemorrhage NOS	1	—	1	—
Worst degree	13	1	18	0

NOS, not otherwise specified.

Events considered to be potentially related to diverticulitis and observed at grade 3 or higher are summarized in Table 3. There were 96 patients affected, including all grades, and 32 patients with events of grade 3 or 4. With regard to only this subset of events, the profile did not differ by arm ($p = 0.71$).

Progression-Free Survival

All 162 patients were included in the efficacy analysis, which is essentially an evaluation of the combination of induction and maintenance between the two randomized groups. There were 149 events among these patients. Across both arms, median PFS was 4.5 months (95% confidence interval [CI], 3.6–4.9 months). This was not an improvement over historical control rates, as initially hypothesized. PFS by arm is shown in Figure 2A. Median PFS among patients randomized to vandetanib maintenance was 4.5 months (95% CI, 3.3–5.8 months), and among patients randomized to placebo maintenance was 4.2 months (95% CI, 2.8–4.9 months).

In an exploratory analysis done in the absence of a demonstrated improvement in PFS over historical controls, we tested the difference between arms, using a stratified log-rank test. This difference calculated from randomization was statistically significant relative to the study's planned type I error (stratified log-rank; $p = 0.07$). We also examined PFS in a multivariable model adjusted for sex and stage. The model is shown in Table 4. After this adjustment, patients randomized to vandetanib maintenance had improved PFS compared with patients randomized to placebo maintenance (hazard ratio = 1.49; 95% CI, 1.07–2.07; Wald $p = 0.02$). ECOG PS and histology were also tested in the model, but they did not contribute prognostic information.

Supplementary Figures 1 and 2 (Supplementary Digital Content, http://links.lww.com/JTO/A431) show PFS by arm, broken up by stage and sex, respectively. Women had longer PFS than men (median 5.1 versus 3.8 months; $p = 0.04$). Differences within treatment subgroups were not statistically significant, but the study was not powered to detect such differences.

Among the subset of patients who began maintenance therapy (essentially a landmark analysis examining the contribution of maintenance vandetanib), there was no difference between the arms in PFS (stratified log-rank $p = 0.46$). The number of patients starting maintenance was, however, much lower than anticipated (58 versus 93).

Response

One complete response was observed at 15 months in a patient randomized to vandetanib maintenance. There were 14 partial responses at a median of 4.3 months among patients randomized to vandetanib maintenance and 15 partial responses at a median of 3.1 months among patients randomized to placebo maintenance. The overall response rate was 18.5% (95% CI, 12.9%–25.4%).

Overall Survival

As of January 28, 2011, 105 patients had died. OS is shown in Figure 2B. Median OS among patients randomized to vandetanib maintenance was 9.8 months (95% CI, 7.3–15.7 months). Median OS among patients randomized to placebo maintenance was 9.4 months (95% CI, 7.5–12.2 months). This difference was not statistically significant (stratified log-rank $p = 0.68$).

Supplementary Figures 3 and 4 (Supplemental Digital Content, http://links.lww.com/JTO/A431) show OS by treatment arm within stage and sex subgroups. Median OS was longer for women than for men (median 16.0 versus 8.2 months; log-rank $p = 0.008$). This effect reached statistical significance among patients randomized to placebo maintenance (median 11.9 versus 7.5 months; log-rank $p = 0.02$) but not among those randomized to vandetanib maintenance (median 16.0 versus 9.8 months; log-rank $p = 0.17$).

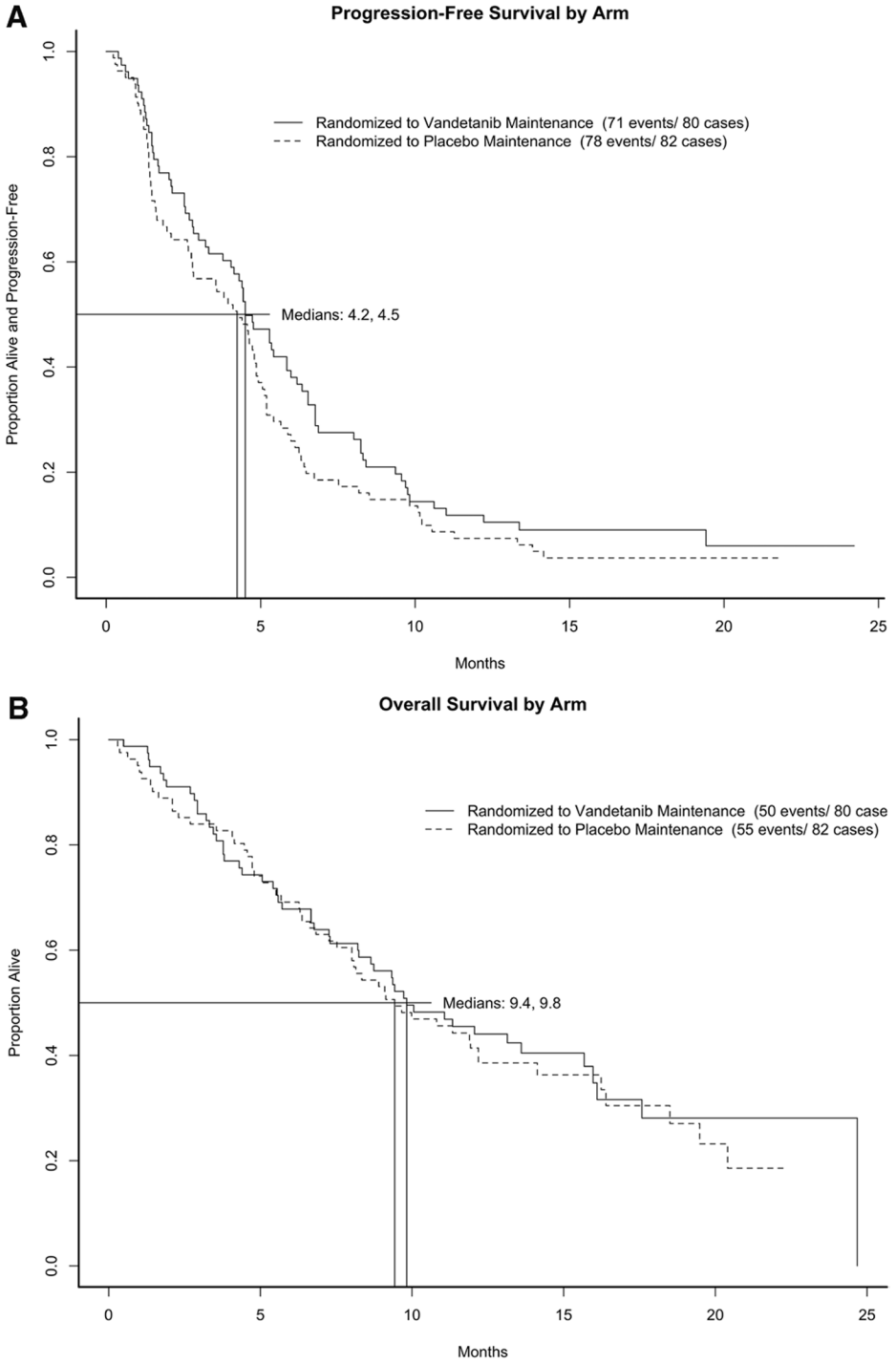

FIGURE 2. *A,* Progression-free survival by randomized maintenance arm. *B,* Overall survival by randomized maintenance arm.

DISCUSSION

The study did not meet the protocol-specified endpoint of improvement over a hypothesized median PFS of 4.6 months. One possible explanation for the poor outcome is that the patient population may have included a higher-than-expected proportion of poor-risk patients. The historical control rate was estimated using the rate observed in the carboplatin/paclitaxel arm of the trial reported by Sandler et al.[6] Our patient population had a slightly lower proportion with stage IIIB disease (10 versus 13%), and also included patients with squamous carcinoma, which may have rendered the control rate optimistic. However, Belani et al.[19] reported median time to progression of 5.4 months in a population of patients, 24% of whom had stage IIIB disease.

The median PFS of 4.5 months observed among patients randomized to vandetanib maintenance is somewhat

TABLE 4. Multivariate Model of Progression-Free Survival

	Hazard Ratio	95% Confidence Interval	Wald *p*
Arm = placebo	1.49	1.07–2.07	0.02
Sex = male	1.37	0.99–1.92	0.06
Stage recurrent vs. IIIB	1.28	0.55–2.96	0.57
Stage IV vs. IIIB	2.62	1.35–5.09	0.005

lower than that observed in other first-line studies. Heymach et al.[20] conducted a randomized phase II study of first-line carboplatin and paclitaxel with or without vandetanib in patients with advanced NSCLC. The study also had a vandetanib monotherapy arm that closed early because of lack of efficacy. In both vandetanib arms, the drug was given at 300 mg/day. As in our study, 90% of patients had stage IV disease. The authors observed longer PFS when vandetanib was added to carboplatin and paclitaxel (median PFS 5.5 versus 5.3 months; log-rank $p = 0.09$). Although the study had no explicit maintenance phase, the authors observed, "the PFS benefit was mainly observed among patients treated for more than 4 months, suggesting that post-chemotherapy maintenance therapy may have contributed to the benefit." The higher dosing of vandetanib during induction (300 mg/day compared with 100 mg/day in our study) may also have contributed to their more favorable outcome, although the 100-mg dosage had been shown in another randomized phase II study to have efficacy similar or somewhat superior to the 300-mg dosage when given with docetaxel to previously treated patients.[17]

The lack of improvement in OS is consistent with recent reports showing no evidence of a survival improvement with vandetanib in NSCLC (e.g., ZEAL,[21] ZEPHYR,[22] ZEST,[23] ZODIAC).[24] Similarly, recent reports of other targeted therapies in NSCLC have failed to demonstrate improved survival (e.g., BeTa,[15] NExUS,[25] ESCAPE,[26] MONET1[27]), despite showing improved PFS (e.g., ATLAS),[16] Our study was not powered to detect a survival difference.

We did not meet the protocol-specified condition for testing for differences in PFS between patients who began vandetanib maintenance and those who began placebo maintenance. However, fewer patients reached maintenance than expected, and our statistical power to detect differences in the PFS was compromised. In our exploratory analysis, prolonged PFS was demonstrated among patients randomized to vandetanib maintenance, using a multivariable model adjusting for sex and stage. Therefore, our favorable comparison of PFS for vandetanib among patients starting maintenance on the two arms should be viewed as hypothesis generating.

The observed toxicity profile was similar to that seen in other trials of cytotoxic chemotherapy in combination with VEGF-targeted therapy. Although there were few events of grade 4 or more during maintenance, adverse events need to be considered when evaluating risks and benefits of vandetanib maintenance. Across all phases of treatment, we observed no hemoptysis, one grade 5 treatment-related hemorrhage, and a grade 5 lung hemorrhage, felt to reflect disease progression. We explored adverse events related to diverticulitis and found that rates were similar between arms. The lack of a defined term for diverticulitis, however, may impede its recognition as a side effect in treatments with targeted therapies.

The proportion of patients who continued to the maintenance phase was lower than expected (38 versus 61%). Approximately a quarter of the patients withdrew during or after induction because of adverse events. In retrospect, protocol criteria for withdrawal may have been more stringent than necessary. For example, bilirubin above the institution's upper limit of normal triggered a dosage reduction, and only one dosage-level reduction was permitted for vandetanib during induction.

The study's ineligibility rate was higher than expected, specifically related to missing or out-of-range values for magnesium, potassium, or calcium. In retrospect, the requirements may have been stricter than necessary to assure patient safety, although seven patients experienced grade 3 and 4 treatment-related adverse events related to low levels of the laboratories, and four of these patients were ineligible because of low levels at baseline.

In 2009, Hanrahan et al.[28] reported that patients with low baseline blood levels of VEGF were more likely to benefit from vandetanib therapy. If confirmed prospectively, this might serve as a biomarker in identifying patients for whom vandetanib therapy might be beneficial. Similarly, EGFR mutation status is a known prognostic or predictive factor. However, no blood samples were collected on this trial to permit exploration of these biomarkers.

There is a growing body of evidence that maintenance targeted therapy improves PFS in patients with NSCLC.[29] We conclude that vandetanib may also have a role as maintenance therapy for patients with NSCLC treated with cytotoxic chemotherapy. Further studies exploring risks, benefits, and potential predictive markers seem justified.

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